Left ventricular non-compaction: Prevalence in congenital heart disease

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Abstract: INTRODUCTION: Left ventricular non-compaction cardiomyopathy (LVNC) is a rare cardiomyopathy, originally described as an isolated disease without other structural cardiac abnormalities. The aim of this study was to explore the prevalence of LVNC among adults with different types of congenital heart disease. METHODS: From our databases we identified adults with congenital heart disease who fulfilled diagnostic criteria for LVNC. We report frequencies of associated congenital cardiac defects and the prevalence of LVNC among patients with different congenital heart defects. RESULTS: From a total of 202 patients with LVNC, 24 patients (12%; mean age 32±11years, 19 males) had additional congenital cardiac defects. Associated defects were left ventricular outflow tract abnormalities in 11 patients (46%), including 7 uni- or bicuspid aortic valves; two aortic coarctations; one diffuse aortic hypoplasia and one subaortic stenosis, Ebstein anomaly in 6 patients (25%), tetralogy of Fallot in two (8%), and double outlet right ventricle in one patient (4%). In our cohort, the prevalence of LVNC was highest among patients with Ebstein anomaly (6/40, 15%), followed by aortic coarctation (2/60, 3%), tetralogy of Fallot (3/129, 2%) and uni- or bicuspid aortic valves (7/963, 1%). CONCLUSION: In adults, various forms of congenital heart disease are associated with LVNC, particularly stenotic lesions of the left ventricular outflow tract, Ebstein anomaly, and tetralogy of Fallot. In the future, studying these patients in more depth may provide a better understanding of the interplay between genetic and hemodynamic factors that lead to the phenotype of LVNC.

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Left Ventricular Non Compaction:

Prevalence in Congenital Heart Disease

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ABSTRACT

Introduction: Left ventricular non-compaction cardiomyopathy (LVNC) is a rare cardiomyopathy, originally described as an isolated disease without other structural cardiac abnormalities. The aim of this study was to explore the prevalence of LVNC among adults with different types of congenital heart disease.

Methods: From our databases we identified adults with congenital heart disease who fulfilled diagnostic criteria for LVNC. We report frequencies of associated congenital cardiac defects and the prevalence of LVNC among patients with different congenital heart defects.

Results: From a total of 202 patients with LVNC, 24 patients (12%; mean age 32±11 years, 7 females, 17 males) had additional congenital cardiac defects. Associated defects were left ventricular outflow tract abnormalities in 11 patients (46%), including 7 uni- or bicuspid aortic valves; two aortic coarctations; one diffuse aortic hypoplasia and one subaortic stenosis, Ebstein anomaly in 6 patients (25%), tetralogy of Fallot in two (8%), and double outlet right ventricle in one patient (4%). In our cohort, the prevalence of LVNC was highest among patients with Ebstein anomaly (6/40, 15%), followed by aortic coarctation (2/60, 3%), tetralogy of Fallot (3/129, 2%) and uni- or bicuspid aortic valves (7/963, 1%).

Conclusion: In adults, various forms of congenital heart disease are associated with LVNC, particularly stenotic lesions of the left ventricular outflow tract, Ebstein anomaly, and tetralogy of Fallot. In the future, studying these patients in more depth may provide a better understanding of the interplay between genetic and hemodynamic factors that lead to the phenotype of LVNC.

INTRODUCTION

Since its first description, left ventricular non-compaction (LVNC) cardiomyopathy has gained increasing awareness and attention. [1-3] By its original definition[4], the absence of other structural heart disease is a prerequisite for the diagnosis of LVNC cardiomyopathy. The clinical presentation and outcome of patients with isolated LVNC is variable. Symptomatic patients have an adverse long-term outcome, while outcome in asymptomatic patients seems to be more favourable. [5-15] Typical complications include congestive heart failure, ventricular arrhythmias and thromboembolic events.[12-14,16,17]

Recently, the association of LVNC with metabolic diseases, genetic syndromes and other cardiac abnormalities has been reported. [18-20] Genetic studies have shown sarcomere gene mutations in some patients with isolated LVNC similar to those with dilated or hypertrophic cardiomyopathy, and a recent study has found similar mutations in patients with Ebstein anomaly. [21,22] There is, however, no clear genotype–phenotype association. [23] Genetic abnormalities may thus cause both structural congenital malformations and impaired left ventricular myocardial differentiation. Alternatively, hemodynamic alterations during fetal life may be a co-factor for the development of ventricular non-compaction in a patient with genetic predisposition. [24,25]

The purpose of this study was to explore the association between congenital heart defects and LVNC and to report its prevalence within adults with a distinct type of congenital cardiac defect.

METHODS

Patients

From January 1987 to November 2011 all patient, who fulfilled diagnostic criteria for LVNC were identified from our clinical echocardiographic database. While there are no generally accepted diagnostic criteria for LVNC, for the purpose of this study, we used echocardiographic criteria as proposed by our group.[4,5] These criteria have been shown to identify a subset of symptomatic patients at risk for adverse outcome. [15] In brief, the criteria include a combination of 1) segmental thickening of the left ventricular myocardial wall 2) consisting of an inner non-compacted and an outer compacted layer with 3) a thickness ratio ≥ 2:1 at end-systole, measured in the parasternal short-axis view, and 4) presence of deep recesses with evidence of blood flow from the ventricular cavity by color Doppler. No other imaging modality was used for diagnosis in this study. Patients identified with LVNC were cross-linked with our congenital cardiac database to identify subjects with both, congenital heart disease and LVNC and to determine the frequency of LVNC among patients with individual congenital cardiac disease entities.

Baseline characteristics included demographic characteristics at last follow-up, exact anatomical cardiac diagnoses, previous surgical and non-surgical treatment history, previous cardiovascular complications and left ventricular function at last follow-up.

This manuscript also complies with the Principles of Ethical Publishing in the International Journal of Cardiology.[26]

Echocardiography

Transthoracic two-dimensional echocardiography was performed using commercially available equipment. Left and right ventricular dimensions and function

were assessed according to established guidelines for two-dimensional echocardiography. [27]

Statistical analysis

Continuous variables are presented as mean ± standard deviation, and medians and ranges as appropriate. Categorical variables are given as frequencies and percentages. All statistical analyses were performed with the use of SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Patients

We identified a total of 202 patients with LVNC, of whom 24 (12%) had associated congenital cardiac defects. These 24 patients comprised the study group. All study patients were diagnosed with LVNC at their first visit in the adult clinic. We did not observe patients who fulfilled diagnostic criteria during follow-up only. Nineteen (79%) were males and median age at last follow-up was 31 years (range 24-44). Two patients (8%) had a family history of LVNC. None of the patients in this cohort had a known syndromic association. *Table 1* illustrates types of congenital cardiac defects, previous surgical procedures and data about left ventricular dimensions and systolic function at last follow-up.

As illustrated in *figure 1A* the most common associated congenital cardiac defects were different forms of left ventricular outflow tract abnormalities and/or obstruction (11/24, 46%), including 7 patients with uni- or bicuspid aortic valves; 2 patients with aortic coarctation 1 patient with diffuse hypoplasia of the aorta and 1 patient with subaortic stenosis. The second largest group were patients with Ebstein

anomaly of the tricuspid valve (6/24, 25%), followed by patients with tetralogy of Fallot or double outlet right ventricle of Fallot-type (3/24, 13%). Typical case examples of patients with these three congenital cardiac disease entities are illustrated in *figures 2-4*.

Previous cardiovascular complications

Twenty-three patients (96%) were in sinus rhythm and 1 patient (4%) was in permanent atrial fibrillation. One patient (4%) suffered a stroke at age 39 years, of potentially cardioembolic cause (patient 15). Seven patients (29%) had a history of supraventricular tachycardia. These included 4 patients with atrial flutter or fibrillation and 3 patients with Ebstein-anomaly and concomitant Wolff-Parkinson-White syndrome with associated AV- reentrant tachycardia). Two patients had a history of sustained ventricular tachycardia (one patient with tricuspid valve dysplasia in the setting of severe tricuspid regurgitation and 1 patient with Ebstein-anomaly of the tricuspid valve). One patient with poor left ventricular ejection fraction (patient 19 in table 1) was treated for symptomatic congestive heart failure.

Echocardiographic features

Mean left ventricular ejection fraction was 52±9% (range 24-61%). 9 patients (37%) had a left ventricular ejection fraction <52% and 3 patients (13%) had dilated left ventricles. Left ventricular diastolic dysfunction was detected in 4 patients (17%). Left ventricular segments most commonly involved were apical (23/24, 96%) midventricular inferior (9/24, 38%) and midventricular lateral (9/24, 38%). In 1 patient (table 1 – patient 22, figure 4) markedly abnormal right ventricular myocardium was noted, suggesting right ventricular involvement.

Prevalence of left ventricular non-compaction among different congenital cardiac defects

As illustrated in *figure 1B*, the prevalence of LVNC in patients with a distinct congenital heart defect was significantly different between different congenital cardiac lesions. The prevalence of patients with concomitant LVNC was highest among patients with Ebstein anomaly (6/40, 15%), followed by aortic coarctation (2/60, 3%), tetralogy of Fallot (3/129, 2%) and uni- or bicuspid aortic valves (7/963, 1%) ($p < 0.001$ for comparison between groups).

DISCUSSION

In this study of adults with congenital heart disease we report types of congenital cardiac defects most commonly associated with LVNC and report prevalence of LVNC among these congenital cardiac disease entities. The most common congenital cardiac defects associated with LVNC were various forms of left ventricular outflow tract abnormalities and obstructions, Ebstein anomaly and tetralogy of Fallot. The prevalence of LVNC was highest for Ebstein anomaly followed by aortic coarctation, tetralogy of Fallot, and bicuspid aortic valves.

Recently, it has been shown in a pediatric series that left ventricular non-compaction with associated congenital heart disease confers additional risk. [28] While our study is too small to assess the effect of LVNC on cardiac outcomes in patients with congenital heart disease, our observations raise a number of hypotheses

regarding the development of LVNC in patients with and without concomitant congenital heart lesions.

Ebstein anomaly is thought to be caused by failure of right heart differentiation in such that the tricuspid valve leaflets do not delaminate properly from the myocardial mass during embryologic development. The association of Ebstein anomaly and LVNC has been reported. [29] A recent study has found similar sarcomeric gene mutations in patients with Ebstein anomaly and in patients with isolated forms of LVNC. [22] This suggests that a similar genetic predisposition may lead to both, defective right and left ventricular myocardial differentiation with different morphologic-phenotypic manifestations. Comparable mechanisms may play a role in patients with conotruncal defects in whom the outflow tract of both, the right and left ventricle, and thus differentiation of right and left ventricular myocardial mass may be abnormal.

On the other hand, LVNC in the setting of congenital left ventricular outflow tract obstruction may be a model for the interplay between hemodynamic factors that trigger abnormal left ventricular differentiation in a genetically susceptible individual. Indeed, the variability of hereditary patterns in LVNC raise the question whether LVNC reflects a primary abnormality in the early myocardial morphogenesis or develops pre- or even postnatal due to additional triggers and modifiers, such as pressure overload on the developing left ventricle due to outflow tract obstruction.

Better characterization of genetic mutations and phenotypic abnormalities in left ventricular development in patients with LVNC and congenital heart disease may therefore have an important role for a better understanding of pathophysiology and development of LVNC in patients without associated congenital heart disease. Whether LVNC in association with other pathologies has a similar or different genetic

basis, pathobiology, and natural course, and whether different mechanisms account for different entities of LVNC remains a matter of further research.

As there may be a genetic susceptibility for abnormal myocardial development in patients with LVNC in the setting of congenital heart defects, it may be wise to offer family screening to relatives of these patients in order to identify yet asymptomatic patients with LVNC that may be at risk for future deterioration.[16]

As in all series of patients with LVNC the absence of generally accepted diagnostic criteria for this disease entity remains a dilemma. While the criteria proposed by our group may be too sensitive, particularly in black individuals, they may identify symptomatic patients of a Caucasian population at high risk for cardiovascular complications.

The hypotheses raised in the discussion section of this paper remain unproven, as formal genetic testing is missing in this and other patient cohort. Further studies will be needed to validate these issues.

In patients with LVNC and left ventricular outflow tract obstructions, LVNC must be differentiated from persisting myocardial sinusoids with connection to the coronary circulation, a well-known abnormality of coronary artery differentiation in patients with high endoventricular pressures during embryological development. Although there was no evidence of such sinusoids with connection to the coronary arteries in any of the patients included into this cohort, not all patients had undergone selective coronary angiography or angiograms were not available for review.

The number of affected patients within this series is small. Thus, to determine the impact of the additional presence of LVNC on cardiovascular outcomes in affected patients with congenital heart disease, larger cohorts with long-term follow-up are needed. Ideally, these patients should be followed in a multicenter registry to further evaluate characteristics and outcomes of LVNC in the setting of different

forms of congenital heart disease and to assess the impact of LVNC on cardiovascular outcomes in patients with congenital heart disease.

In this study we used only echocardiography for the diagnosis of LVNC. In the future, other imaging modalities, such as cardiac magnetic resonance imaging or computed tomography may be useful for diagnosis of LVNC in patients with suboptimal acoustic windows on echocardiography.

In conclusion, various forms of congenital heart disease may be associated with LVNC, particularly stenotic lesions of the left ventricular outflow tract, Ebstein anomaly, and tetralogy of Fallot. In the future, studying these patients in more depth may provide a better understanding of the interplay between genetic and hemodynamic factors that lead to the phenotype of LVNC.

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Figure Legends

Table 1: Anatomical characteristics, previous surgeries and left ventricular dimensions and function

Abbreviations: LVEF: Left ventricular ejection fraction; EDVI: Left ventricular enddiastolic volume indexed to body surface area

Figure 1: A: Proportional distribution of patients with LVNC and congenital heart disease within the study cohort. **B**: Prevalence of LVNC among the most commonly affected congenital cardiac lesions

Figure 2: LVNC in left ventricular outflow tract obstruction. 18-year old patient with bicuspid aortic valve, hypoplastic aortic annulus (no systolic pressure gradient in LVOT), hypoplastic left ventricle and secundum type atrial septal defect. Panel A shows a 4-chamber view on cardiac magnetic resonance imaging depicting the small left ventricular cavity with abnormal trabeculations with deep recessi of the left ventricular lateral wall. Panel B shows right (green curve) and left (red curve) ventricular inflow velocities, recorded on cardiac magnetic resonance imaging, illustrating the abnormal filling pattern of the left ventricle. Panel C and D show short axis view of the left ventricle on cardiac magnetic resonance imaging (panel C) and the corresponding image on echocardiography (panel D).

Figure 3: LVNC in Ebstein anomaly of the tricuspid valve. 40-year old patient with Ebstein anomaly and secundum type atrial septal defect. Panel A and B depict markedly thickened apikal and lateral left ventricular wall with perfused recessi. Panel

C and D show still frames during injection of agitated saline into the right cubital vein (panel C before and panel D immediately after appearance of bubble contrast into the right atrium). Massive right-to-left shunt without Valsalva-manoeuvre suggests high right sided filling pressures.

Figure 4: LVNC in Fallot-type double outlet right ventricle. 27-year old patient with repaired double outlet right ventricle of Fallot-type. Panel A shows the apical 4-chamber view with highly trabeculated left ventricular apex and panel B a parasternal short axis view below the level of the papillary muscles with the typically thickened, two-layered left ventricular lateral wall. Panel C shows the highly trabeculated right ventricle suggesting right ventricular involvement.